Claims 26-28 are cancelled herein as required by Examiner at paragraph 2 of the Office Action, paper number 13; Claims 21-22 are also cancelled herein to render moot an allegation of anticipation under 35 U.S.C. § 102(b). All of these claims are cancelled solely to advance the prosecution of the present application and without prejudice to pursuing the cancelled claims in this or other divisional or continuing applications.

The specification is amended to correct informalities of typographical errors and punctuation in the long paragraph at page 9 through page 13, as requested by Examiner at paragraph 5 of the Office Action. A marked-up version of the specification is attached hereto as Exhibit A. Although no formal objection to the specification was raised with regard to these informalities, Applicant submits respectfully that the informalities have been corrected and any objection to the specification in their regard has been overcome. No new matter has been added.

New objections to the specification were raised in paragraph 18 of the Office Action under 35 U.S.C. § 132 for the alleged introduction of new matter into the specification by Applicants' amendment of May 14, 2002, paper number 12. In particular, the recitation of certain ranges in Claims 4, 9, 12, 14, 16, and 24 were objected to as new matter. Without acquiescing in the propriety of the objections, Applicants have amended Claims 4, 9, 12, 14, 16, and 24 to recite range values finding clear support in the specification as filed. Respectfully, Applicant directs Examiner's attention to page 7 of the specification as filed and, in particular, lines 16, 24, and 28 thereof which recite ranges for therapeutically effective amounts of serine protease inhibitors under methods of the present invention, and lines 8-9 of page 8, which recite administration regimens. Applicants submit respectfully that the dosage ranges and regimens of administration recited in Claims 4, 9, 12, 14, 16, and 24 find clear and unambiguous support within the cited lines of the specification as filed.

In particular, Applicants submit respectfully that the recitation of "at least .001 and no greater than 70 g/kg body weight" found in Claim 4, as amended, finds support at page 7, line 28 of the specification as filed. Although the specification recites the two overlapping ranges of .001-7.0 sg/kg, for α_1–antitrypsin-like agent, and 1-70 g/kg, for α_1–antitrypsin, of body weight, Applicants submit respectfully that, inasmuch as the scope of Claim 3, from which Claim 4 depends, includes both α_1–antitrypsin and α_1–antitrypsin-like agent, the unification of both ranges for the purpose of reciting an effective range is appropriate in Claim 4.

Applicants submit respectfully that the recitation of "at least .001 and no greater than 7.0 g/kg body weight" found in Claim 9, as amended, finds support at page 7, line 28 of the specification as filed. Applicants submit respectfully that the recitation of "at least 10 pM and no greater than 2 mM" found in Claim 12, as amended, finds support at page 7, line 16 of the specification as filed. Applicants submit respectfully that the recitation of "at least .5 μM and no greater than 200 μM" found in Claims 14 and 24, as amended, finds support at page 7, line 24 of the specification as filed. With respect to the recitation of "at least once daily and no more than once hourly" in Claim 16, Applicant submits respectfully that support for this phrase is found at page 8, lines 8-9, of the specification as filed.

With respect to all of Claims 4, 9, 12, 14, 16, and 24, Applicants submit respectfully that the use of the range terminology "at least" and "no greater than (no more than)," although not recited explicitly in the cited lines of the specification, is acceptable alternative terminology for describing the ranges recited within the specification as filed. Applicants choose this terminology to make clear that the ranges recited are inclusive of the endpoints recited. The specification uses the terminology "between about," and, as Examiner has objected previously to the use of the term "about," Applicant are required to find different terminology to describe

the ranges. Applicant submits respectfully that a range described using the term "between about" should be deemed inclusive of the recited endpoints inasmuch as "about" implies a discrepancy from the exact number recited, and any discrepancy above and below the recited range endpoints will place the endpoints within a range "between" the discrepant figures.

Accordingly, in light of the foregoing, Applicant submits respectfully that the objections to Claims 4, 9, 2, 14, 16, and 24 under 35 U.S.C. § 132 for the alleged introduction of new matter into the specification by Applicants' amendment of May 14, 2002, Paper Number 12, have been overcome, and Applicants request respectfully that the objections to Claims 4, 9, 2, 14, 16, and 24 under 35 U.S.C. § 132 be withdrawn.

As required in paragraph 5 of the Office Action, Claims 8 and 25 have been amended to correct informalities of typographical errors and punctuation. No new matter has been added. Applicant submits respectfully that the objection to the Claims 8 and 25 has been overcome, and Applicant requests respectfully that the objection to Claims 8 and 25 be withdrawn. Please note that a copy of the pending claims in clean form is attached as Exhibit C.

Claims 1-17 were objected to in the Office Action, at paragraph 19, for having a duplication in the Markush group. As required by the Office Action, Claim 1 has been amended to delete one instance of the term "arthritis." No new matter has been added. Applicant submits respectfully that the objection to the Claims 1-17 has been overcome, and Applicants request respectfully that the objection to Claims 1-17 be withdrawn.

Claim 1 has been amended to point out more particularly and claim more distinctly that which Applicant regards as his invention by removing the allegedly overlapping species under the term "wasting disease" from the Markush group in Claim 1, as requested by Examiner.

Claim 3 is amended herein to remove references to "an α_1-antitrypsin-like agent, a variant of α_1-antitrypsin, an anticathepsin G agent, an antitryptase TL-2 agent, an antifactor Xa agent, an antielastase agent, and an antiproteinase-3 agent," and to insert reference to "an oxidation-resistant or free radical-resistant variant" α_1-antitrypsin. Support for the inserted reference is found in the specification as filed at page 5, line 24, to page 6, line 9. Thus, no new matter has been added.

Claim 18 is amended herein to remove the phrase "exhibiting a mammalian α_1-antitrypsin or α_1-antitrypsin-like activity" and to insert "serine protease inhibitor." Support for the amendment is found throughout the specification and claims as filed.

Claim 19 is amended herein to replace the term "inhibiting" with "reducing" as required by Examiner.

Claim 25 is amended herein to incorporate the relevant limitations of cancelled Claims 21 and 22, and Claim 23 is amended herein to redefine it dependency so that it now depends from Claim 25. No new matter has been added.

New Claim 29 has been added. New Claim 29, depending from Claim 1, specifies and claims types of wasting diseases that are encompassesd by the term "wasting disease" from the Markush group in Claim 1. Support for the new claim is found at page 14, lines 5-6, of the specification as filed and, thus, does not represent new matter.

New Claim 30 is added herein. Support for this claim is found in the specification as filed at page 6, lines 29-30. Thus, no new matter has been added.

A marked-up version of the claims indicating the changes to the claims is attached hereto as Exhibit B. A copy of all pending claims, as amended, is attached hereto as Exhibit C. The

amendments are supported fully by the claims and/or specification as originally filed and, thus, do not represent new subject matter.

Applicant wishes to take this opportunity to thank Examiner for Examiner's withdrawal of the objections to specification, as noted in paragraph 4 of the Office Action, and the withdrawal of the various rejections to claims under 35 U.S.C. § 112 noted in paragraphs 6-11 of the Office Action.

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

I. The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Office Action, at paragraph 17, rejects Claims 21-22 as allegedly being anticipated by van Molle *et al.*, J. Immunology 159:3556-3564 (1997)(hereinafter, "van Molle"), under 35 U.S.C. § 102(b). The Office Action alleges that van Molle teaches the use of antitrypsin and subsequent measurement of a decrease in apoptosis. Applicant traverses respectfully.

Without acquiescing in the propriety of the rejection, and solely to advance prosecution of the present application, Applicant has amended the claims by deleting Claims 21 and 22, incorporating the relevant limitations of Claims 21 and 22 into Claim 25, and redefining the dependency of Claims 23 and 24 so that they depend from Claim 25, as amended. Applicant submit respectfully that van Molle does not teach, suggest, or motivate the skilled artisan to practice the reduction of apoptosis by the use of the serine protease inhibitors or oxidation-resistant or free radical-resistant variant of α_1-antitrypsin listed in Claim 25, as amended.

Applicant submits respectfully that, as noted in section III(A), below, support for the inserted reference to "an oxidation-resistant or free radical-resistant variant" of α_1-antitrypsin in place of the Markush group found in previous Claim 22 is found in the specification as filed at page 5, line 24, to page 6, line 9. Thus, no new matter has been added.

Applicant submits respectfully that the rejections to Claims 21-22 under 35 U.S.C. § 102(b) have been rendered moot by the deletion of those claims. Accordingly, Applicant requests respectfully that the rejections to Claims 21-22 under 35 U.S.C. § 102(b) be withdrawn.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

A. Rejection Of Claims 1-18 At Paragraph 14 Of The Office Action

At paragraph 14 of the Office Action, Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action alleges that one of skill in the art would be required to perform undue experimentation to practice the claimed methods to the full extent of their scope due the cause vs. effect nature of disease and apoptosis in general. Applicants traverse respectfully.

Applicants submit respectfully that the test for enablement is whether one of ordinary skill in the art could make or use the claimed invention, without undue experimentation, based on the disclosure in the patent application coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1998). Enablement is not precluded even if some experimentation is necessary. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied*, 480 U.S.

947. This is so even if the amount of experimentation required is laborious. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Furthermore, Applicants submit respectfully that if the specification contains a statement with a connotation of how to use the claimed invention, 35 U.S.C. § 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). When a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention (M.P.E.P. § 2164.01(c), Seventh Ed., February 2000).

Applicants respectfully submit that the pending claims are fully compliant with the above, and are therefore enabled under 35 U.S.C. § 112, first paragraph.

With regard to the rejection of Claims 1-18 under 35 U.S.C. § 112, first paragraph, on the basis that one of skill in the art would allegedly be required to perform undue experimentation to practice the claimed methods to the full extent of their scope due to the alleged cause vs. effect nature of disease and apoptosis in general, Applicant respectfully draws the Examiner's attention to the attached Declaration of Dr. Leland Shapiro ("Shapiro Declaration") and accompanying Appendices A-M describing in detail, firstly, the nature of the established link between disease and apoptosis and secondly, the results of recent *in vitro* and *in* vivo animal experiments, which demonstrate the use of Alpha-1-Antitrypsin in blocking pharmacologically induced programmed cell death or apoptosis. Entry of the Shapiro Declaration and consideration of the evidence presented therein is respectfully requested. At the outset, Applicant respectfully submits that one skilled in the art following the teachings of the specification as filed, coupled with the evidence

provided herein by way of the Shapiro Declaration, would be able to more than adequately practice the claimed invention without undue experimentation.

In particular, the exhaustive list of publications described at paragraphs 4-13 of the Shapiro Declaration clearly demonstrate that, contrary to the Office Action's position, there is indeed a causal link between disease and apoptosis. Applicant respectfully points out, for illustration purposes only, that a linkage has been established between apoptosis and each of the following diseases, including for example, and without limitation, wasting disease, neurodegenerative disease, myocardial infarction, stroke, Alzheimer's disease, arthritis, muscular dystrophy, Downs Syndrome, sepsis, HIV infection, multiple sclerosis, arteriosclerosis, diabetes, arthritis, autoimmune disease, ischemia-reperfusion injury, or toxin-induced liver injury. Moreover, the *in vivo* experiments described at paragraphs 15-23 of the Shapiro Declaration show that the addition of Alpha-1-Antitrypsin was completely effective in blocking pharmacologically induced programmed cell death (or apoptosis induced in rats) by adminstration of SU5416 (SUGEN compound, or 3-[2,4-dimethylpyrrol-5-yl)methylidenyl]-indolin 2-one).

Applicant respectfully submits that the manuscripts provided in the attached Shapiro Declaration provide references that demonstrate that apoptosis is indeed an important contributor to the disease states specifically referred to therein. In view of the established link between apoptosis and disease in general, Applicant respectfully submits that it is therefore rational that an inhibitor of serine proteases (such as Alpha-1-Antitrypsin or an Alpha-1-Antitrypsin-like drug) can indeed be used to treat these diseases without resort to undue experimentation. Indeed, such an apoptosis inhibitor as Alpha-1-Antitrypsin or an AAT-like natural molecule or an AAT-like synthetic mimic would be desirable in those conditions characterized by excessive cell

death; such as wasting disease, neurodegenerative disease, myocardial infarction, stroke, Alzheimer's disease, arthritis, muscular dystrophy, Downs Syndrome, sepsis, HIV infection, multiple sclerosis, arteriosclerosis, diabetes, arthritis, autoimmune disease, ischemia-reperfusion injury, or toxin-induced liver injury.

By way of illustration, Applicant respectfully submits that the publication of Hetts Steven W. described in Paragraph 4 of the Shapiro Declaration is a review article that underscores the role of apoptosis in several diseases. Similarly, Grodzicky Tamara *et al.* described in Paragraph 5 of the Shapiro Declaration contains an article underscoring a role for apoptosis in the generation of rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosis ("lupus"), systemic lupus erythematosis ("lupus"), systemic sclerosis, Sjogren's Syndrome, antiphospholipid syndrome, osteoporosis, osteoarthritis, and the seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatuc arthritis). The publication of Honig Lawrence S. *et al.* described in Paragraph 6 of the Shapiro Declaration contains an article demonstrating that apoptosis likely plays a role in several neurodegenerative diseases. These include (but are not limited to) Parkinson's disease, Alzheimer's disease, Huntington' s disease, amyotrophic lateral sclerosis ("Lou Gehrig's Disease"), and spinocerebellar ataxias. The manuscript of Mahidhara Raja *et al.* described in Paragraph 7 of the Shapiro Declaration has two manuscripts that demonstrate a role for apoptosis in the pathogenesis of sepsis. Therefore, the administration of anti-apoptosis inhibitors ofhost-derived serine proteases may be capable of treating sepsis.

The publications of Williams R. Sanders and James Thomas N. described in Paragraph 8 of the Shapiro Declaration are two articles showing that apoptosis likely has a role in several important cardiovascular diseases. These diseases include (but are not restricted to) acute

myocardial ischemia (angina pectoris), acute myocardial infarction ("heart attack"), thrombotic thrombocytopenic purpura (TTP), arrhythmogenic right ventricular dysplasia, long QT syndromes, and heart failure due to cardiomyopathy (including ischemic, dilated, infiltrative, and hypertrophic cardiomyopathies).

The publication of Ueda Norishi *et al.* described in Paragraph 9 of the Shapiro Declaration shows that apoptosis likely serves as a cause of acute renal failure, and that inhibitors of host-derived serine proteases may be used to treat acute renal failure. Specific diseases that can cause acute renal failure and that possess a component of apoptosis-induced damage include (but is not restricted to) renal failure due to hypoperfusion (ischemia of the kidney or pre-renal azotemia), renal artery stenosis, sepsis, acute renal failure due to contrast media exposure, endotoxin-induced renal failure, oxidant-stress-induced acute renal failure, and toxin or drug-induced acute renal failure (due to antibiotics, chemotherapy agents, immunouppressive drugs, heavy metals, diuretic drugs). Also, apoptosis inhibition may be used as a mode of therapy to treat acute and chronic renal graft (transplant) rejection.

The article of Rust Christian *et al.* described in Paragraph 10 of the Shapiro Declaration contains an article that shows that apoptosis is likely involved in liver disease. Therefore, serine protease inhibition (using AAT or an AAT-like natural molecule or an AAT-like synthetic mimic) may be used to treat liver disease. Specific diseases include alcoholic hepatitis, drug or toxin-induced hepatitis, viral hepatitis (due to hepatitis A, B, C, D, or E), and liver damage due to hypoperfusion ("shock liver", as occurs, for example, in the course of septic shock).

The articles of Aprikyan AG *et al.* and Ancliff Phil J. *et al.* described in Paragraph 11 of the Shapiro Declaration address two papers that discuss two related diseases called cyclic neutropenia and congenital neutropenia. These two diseases manifest as severe reductions in

blood neutrophil amounts, and this is caused by excessive programmed cell death (apoptosis) of the neutrophils. This disease has been found to be due to defects of neutrophil elastase (NE). NE is a host-derived serine protease. The mutations are gain of function variants of NE. Therefore, excessive activity of a host-derived serine protease (NE) can cause apoptosis. Thus, it is rational that inhibition of host-derived serine protease activity using a serine protease inhibitor (such as AAT or an AAT-like natural molecule or an AAT-like synthetic mimic) reduces apoptosis.

The article of Bogdan Inja *et al.* described in Paragraph 12 of the Shapiro Declaration shows that serine protease inhibition may be used to treat meningitis. As described, bacterial meningitis causes apoptosis of brain cells. Therefore, apoptosis inhibition using serine protease blockade is expected to reduced meningitis-associated brain cell death, resulting in clinical improvement.

Finally, U.S. Patent No. 6,489,308 described in Paragraph 13 of the Shapiro Declaration demonstrates the ability of Alpha-1-Antitrypsin or an Alpha-1-Antitrypsin-like synthetic mimics (i.e., CE-2072) to inhibit nitric oxide production as additional support for this mode of treatment, since NO is a well-established mediator of sepsis-induced organ dysfunction and of systemic hypotension. Thus, there are at least two mechanisms by which serine protease inhibition may treat sepsis; namely by inhibition of apoptosis and inhibition of NO production.

Thus, Applicant respectfully submits that each of the above-recited publications more than adequately demonstrate that the claimed invention is enabled across a broad spectrum of diseases thus validating the overall concept that apoptosis can be detrimental to organ function, and that apoptosis inhibition by use of apoptosis inhibitors such as using AAT or similar natural agent or a synthetic AAT-like mimic can indeed be used to treat these diseases.

Moreover, Applicant respectfully submits that the experiments as described beginning at Paragraph 14 of in the Shapiro Declaration demonstrate the use of Alpha-1-Antitrypsin in blocking pharmacologically induced program cell death or apoptosis. The goal of the *in vivo* experiments was to determine whether or not Alpha-1-Antitrypsin would selectively decrease apoptosis, as measured by two histological-based assays and one terminal deoxynucloetideyl transferase-mediated assay known to those of skill in the art as providing key indicators of apoptosis. The first histlogical assay is the PCNA lung immunohistochemistry assay. The second histological assay is the Mean Linear Intercept (MLI) Assay. The third assay is the terminal deoxynucloetideyl transferase dUTP nick end-labeling (TUNEL) Assay. Each of the three assays are disclosed in the article authored by Kasahara *et al.* (Kasahara *et al* JCI Vol. 106:11 pp1311-1319).

The PCNA lung immunohistochemistry assay, admistration of SU5416 to rats preferentially induces apoptosis and causes the dissapearance of alveolar septal structures resulting in emphysema and concommitant alveolar cell death and is comparable to the loss of precapillary arterioles in the treated rats.

The MLI Assay is a measure of interalveolar wall distance. In the MLI Assay, Admistration of SU5416 to rats preferentially induces apoptosis as evidenced by significantly greater interalveolar wall distances indicating that the SU5416-treated lungs were emphysemous, i.e., there was a loss of alveolar septa, compared to animals not receiving the SU5416 drug. The process itself can be characterized by the absence of increased filtration by inflammatory cells as assessed by light microscopic examination of hematoxylin and eosin-stained slides and antimacrophage immunistaining, or fibrosis in SU5416-treated rat lungs compared to control lungs.

The TUNEL Assay technique is used to detect apoptosis and relies on labeling of DNA strand breaks in situ as evidenced by increased levels of terminal deoxynucloetideyl transferase dUTP nick end-labeling of cells localized to the peribronchiolar, intra-alveolar, and septal cells.

The results depicted in paragraph 19 in Table 1 (Appendix O) of the Shapiro Declaration, which presents the results of six separate experiments, unequivocally demonstrate that the addition of Alpha-1-Antitrypsin was effective in inhibiting or blocking pharmacologically induced programmed cell death (or apoptosis induced in rats) by adminstration of SU5416, as measured by the MLI Assay. Animals receiving SU5416 alone showed increased apoptosis as revealed by the significantly higher MLI interalveolar wall distance measurements (i.e., 68.94 for SU5416 alone versus 57.51 for SU5416 plus Alpha-1-Antitrypsin). The data presented in Figure 1 (Appendix P) depict the histogram representation of the same results. The inhibitory effect of Alpha-1-Antitrypsin as significantly inhibiting apoptosis is thus clearly evident.

The results depicted in Figure 2A (Appendix Q) of the Shapiro Declaration unequivocally demonstrate that the addition of Alpha-1-Antitrypsin was effective in inhibiting or blocking pharmacologically induced program cell death or apoptosis induced in rats by adminstration of SU5416, as measured by the PCNA lung immunohistochemistry assay. Animals receiving SU5416 alone showed increased apoptosis as revealed by the emphysemous-appearing lungs evident in Figure 2B (Appendix Q). The inhibitory effect of Alpha-1-Antitrypsin as significantly inhibiting apoptosis is thus clearly evident.

Finally, the results depicted in paragraph 21 in Table 2 (Appendix R) of the Shapiro Declaration, which presents the results of four separate experiments, unequivocally demonstrate that the addition of Alpha-1-Antitrypsin was effective in inhibiting or blocking pharmacologically induced programmed cell death (or apoptosis induced in rats) by

adminstration of SU5416, as measured by the TUNEL Assay. Animals receiving SU5416 alone showed increased apoptosis as revealed by the significantly higher TUNEL values. The data presented in Figure 3 (Appendix S) depict the histogram representation of the same results (greater than 14 fold, i.e., 43% for SU5416 alone versus approximately 3% for SU5416 plus Alpha-1-Antitrypsin). The inhibitory effect of Alpha-1-Antitrypsin as significantly inhibiting apoptosis is thus clearly evident.

Therefore, in view of the arguments presented above and the evidence presented in the Shapiro Declaration, Applicant respectfully submits that one skilled in the art following the teachings of the specification as filed, coupled with the evidence provided herein by way of the Shapiro Declaration, would be able to more than adequately practice the claimed invention without undue experimentation. On this basis, Applicant submits respectfully that the rejection of Claims 1-18 under 35 U.S.C. § 112, first paragraph has been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, first paragraph, rejection of Claims 1-18 be withdrawn.

B. Rejection Of Claims 19-20 At Paragraph 15 Of The Office Action

At paragraph 15 of the Office Action, Claims 19-20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action alleges that the term "inhibiting" is not enabled. Applicant traverses respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, Claim 1 is amended herein to substitute the term "reducing" for the term "inhibiting." Applicant respectfully directs Examiner's attention to paragraph 15 of the Office Action in which Examiner acknowledges that the term "reducing" is enabled. On this basis, Applicant submits respectfully that the rejection of Claims 19-20 under 35 U.S.C. § 112, first paragraph has been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, first paragraph, rejection of Claims 19-20 be withdrawn.

C. Rejection Of Claims 21-25 At Paragraph 16 Of The Office Action

At paragraph 16 of the Office Action, Claims 21-25 are rejected under 35 U.S.C. § 112, first paragraph, because while being enabled for using certain serine protease inhibitors to inhibit some form of apoptosis, allegedly does not reasonably provide enablement for using all serine protease inhibitors to inhibit all forms of apoptosis. Applicants traverse respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, Applicant wishes to point out that the accompanying Declaration of Dr. Shapiro clearly demonstrates that the administration to animals, suffering from or experiencing

apoptosis as experimentally induced with SU5416, of AAT, significantly inhibits or blocking unexpectedly and dramatically, pharmacologically induced programmed cell death or apoptosis. Moreover, Applicant respectfully submits that synthetic small molecule mimics of AAT that inhibit host-derived serine proteases have also been shown to inhibit apoptosis. For example, the effect of AAT as inhibiting or reducing programmed cell death or apoptosis is not limited to AAT as Applicant has also demonstrated that a peptoid molecule, CE-2072, also exhibits such activity. Applicant respectfully draws the Examiner's attention to Figure 1 of the above-identitified specification relating to the effect of 1-antitrypsin on apoptosis in primary rat brain cerebral granule cells and Figure 2 illustrating the effect of a1-antitrypsin and the peptoid CE-2072 on apoptosis in RCG Neuron (rat cerebral granule) cells. Applicant also directs the Examiner to Page 15, line 29 through Page 19, line 5 of the specification and more particularly to Example 6.5 on page 17, line 14 – page 18, line 6 which specifically addresses the effect of AAT and CE-2072 on apotosis in RCG neural cells. Applicant respectfully submits that this demonstrates that the apoptosis-inhibiting effect of the natural AAT was, in fact, due to the inhibition of host-derived serine proteases, and not due to some different effect of the natural AAT.

Thus, Applicant respectfully submits that the experiments depicted in the attached Shapiro Declaration uequivocally demonstrate that the administration of an inhibitor of serine protease with AAT or AAT-like biological activity to animals, suffering from or experiencing apoptosis as experimentally induced with SU5416, significantly inhibits unexpectedly and dramatically programmed cell death or apoptosis. Thus, that AAT and synthetic small molecules mimicing AAT biological activities (such as for example, and without limitation, CE-2072) are enabled for the present invention is not in doubt. Applicant respectfully submits that

the particular assays disclosed in the specification and in the Shapiro Declaration provide more than adequate information for one skilled in the art to which the invention pertains to be able to determine whether or not any of the serine protease inhibitors are capable of inhibiting or reducing apoptisis without undue experimentation.

On this basis, Applicant submits respectfully that the rejection of Claims 19-20 under 35 U.S.C. § 112, first paragraph has been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, first paragraph, rejection of Claims 19-20 be withdrawn.

D. Rejection Of Claims 4, 9, 12-14, 16, And 24 At Paragraph 21 Of The Office Action

At paragraph 21 of the Office Action, Claims 4, 9, 12-14, 16, and 24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. The Office Action alleges that the aforementioned claims, as amended, contained matter not described in the specification as filed. Applicant traverses respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, the aforementioned claims are amended herein to recite ranges that find clear and unambiguous support in the specification as filed. The Examiner will please kindly refer to the arguments, in support of overcoming the objections against the same group of claims, already presented above. Accordingly, Applicant submits respectfully that the alleged new matter rejection has been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, first paragraph, rejection of Claims 4, 9, 12-14, 16, and 24 be withdrawn.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

A. Rejection Of Claims 3, 4, And 22-24 At Paragraph 12 Of The Office Action

At paragraph 12 of the Office Action, Claims 3, 4, and 22-24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. The Office Action alleges that the terms "an α_1-antitrypsin-like agent, a variant of α_1-antitrypsin, an anticathepsin G agent, an antitryptase TL-2 agent, an antifactor Xa agent, an antielastase agent, and an antiproteinase-3 agent" are indefinite. Applicant traverses respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, Claim 3 is amended herein to remove the allegedly indefinite terms and to insert reference to "an oxidation-resistant or free radical-resistant variant" of α_1-antitrypsin. Support for the inserted reference is found in the specification as filed at page 5, line 24, to page 6, line 9. Claim 22 is cancelled herein, as noted above, but the amended limitation to "an oxidation-resistant or free radical-resistant variant" of α_1-antitrypsin is incorporated into Claim 25, as amended. Claims 23 and 24 are amended to redefine their dependency so that they now depend from Claim 25, as amended. Applicant submits respectfully that the rejection of Claims 3, 4, and 22-24 under 35 U.S.C. § 112, second paragraph, has been overcome, no new matter has been added, and Applicants request respectfully that the 35 U.S.C. § 112, second paragraph, rejection of Claims 3, 4, and 22-24 be withdrawn.

B. Rejection Of Claim 18 At Paragraph 13 Of The Office Action

At paragraph 13 of the Office Action, Claim 18 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. The Office Action alleges that the phrase "exhibiting mammalian α_1-antitrypsin or α_1-antitrypsin-like activity" is indefinite. Applicant traverses respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, Claim 18 is amended herein to remove the allegedly indefinite phrase and to insert the phrase "serine protease inhibitor," which is defined throughout the specification and claims as filed. Thus, no new matter has been added. Applicant submits respectfully that the rejection of Claim 18 under 35 U.S.C. § 112, second paragraph, has been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, second paragraph, rejection of Claim 18 be withdrawn.

C. Rejection Of Claims 1-17 At Paragraph 20 Of The Office Action

At paragraph 20 of the Office Action, Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter regarded as the invention. The Office Action alleges that some members of the Markush group in Claim 1 overlap one another, rendering the named species confusing. Applicant traverses respectfully.

Without acquiescing in the propriety of rejection, and solely to advance prosecution of the present application, Claim 1 is amended herein to remove the allegedly overlapping species.

Those species are now recited in new Claim 29, depending from Claim 1. On this basis, Applicant submits respectfully that the rejection has been overcome, and Applicant requests respectfully that the 35 U.S.C. § 112, second paragraph, rejection of Claim 1 be withdrawn.

CONCLUSION

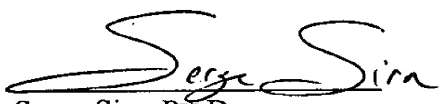
Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



Serge Sira, PH.D.
Registration No. 39.445
Gilberto M. Villacorta, Ph.D.
Registration No. 34,038

Patent Administrator
KATTEN MUCHIN ZAVIS ROSENMAN
525 West Monroe Street, Suite 1600
Chicago, Illinois 60661-3693

Facsimile: (312) 902-1061

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